REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-2, 7-15, 31-32 and 38-40 are pending.

Information Disclosure Statement

To satisfy their continuing duties of candor and good faith, Applicants bring to the attention of the Examiner related subject matter in the U.S. patent application: Serial No. 11/785,591. It is also noted that he found the claimed invention of this application to be patentable over the claimed invention of the '591 application. The Examiner is invited to consider its prosecution history and the prior art of record in that application, which are accessible through the PTO's Image File Wrapper (IFW), in view of the Federal Circuit's holding in *McKesson Information Solutions v. Bridge Medical*, 82 USPQ2d 1865 (Fed. Cir. 2007). To avoid duplication of those materials in the PTO's records, reference to the IFW is encouraged but Applicants would be ready to submit copies of these materials for the Examiner's review if he prefers.

Double Patenting

Claims 1-2, 7-15 and 31-32 were rejected on the ground of nonstatutory obvious-ness-type double patenting as allegedly unpatentable over claims 1-8 of Patent No. 6,277,627. Applicants traverse because their presently claimed invention has properties that are unexpected as compared to the claims of the '627 patent.

The pending claims are directed to a glucose binding protein (GBP) with at least one reporter group attached at one or more of position 10, 93 or 183. None of these positions for attaching a reporter group were mentioned in the claims of the '627 patent. Nor was any relevant evidence or reasoning presented in the Office Action for selecting one or more of these positions from all possible attachments positions in the amino acid sequence of GBP. The Examiner alleged on page 4 of the Office Action that "the cited patented claims encompass all possible attachment positions within the GBP and the disclosure of the cited patent contemplates the same."

But the attachment at one or more of position 10, 93 or 183, which is required by Applicants' claims, is a difference between Applicants' claimed invention and the prior

art that the Examiner failed to address. Here, assuming for the sake of argument that the '627 patent contemplated attachment at any position within GBP, no acceptable evidence or reasoning was provided in the Office Action that support the allegation that one of ordinary skill in the art would have found it obvious to select one or more of position 10, 93 or 183 for attachment as required by Applicants' claims. Here, the claims of the '627 patent and the pending claims are in a genus-species relationship that requires a better reason than it would have been obvious "to utilize any or all of the possible biding sites" as alleged on page 4 of the Office Action. Finally, there was no reasonable expectation of success shown in the Office Action that attaching at least one reporter group at any position within GBP such that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as required by the present claims. For these reasons, a prima facie case of obviousness was not established. Therefore, it would not have been obvious to attach at least one reporter group at one or more of position 10, 93 or 183 within GBP.

Applicants submit that this rejection is substantially the same as the obviousness rejection under Section 103. Therefore, the withdrawal of either rejection should require withdrawal of both rejections.

For the above reasons, withdrawal of the double patenting rejection is requested.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR Int'l v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See

id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hind-sight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396. An inquiry should be made as to "whether the improvement is more than the predictable use of prior art elements according to their established functions." Id. But a claim that is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-2, 7-15 and 31-32 were rejected under Section 103(a) as allegedly unpatentable over Hellinga (WO 99/34212 or US 6,277,627). Claims 1 and 7-15 were also rejected under Section 103(a) as allegedly unpatentable over Amiss et al. (US 2003/01344346 or US 6,855,556). Applicants traverse all four rejections for the same reasons, which are explained below.

Applicants' present claims are directed to a glucose binding protein (GBP) with at least one reporter group attached at one or more of position 10, 93 or 183. See Table 5 at pages 33-34 and 35 of the present specification. Neither Hellinga nor Amiss teaches or renders obvious these specific positions within a GBP for attaching reporter groups. Further, there is no acceptable technical reason provided in the Office Action for why one of ordinary skill in the art would have attached one or more reporter groups at these specific positions within a GBP. The ΔI_{std} and ΔR_{max} properties of the biosensors were experimentally determined by Applicants.

More specifically, attaching a reporter group at amino acid position 183 provides the unexpected results of decreased binding affinity for glucose and increased fluorescence characteristics. For a person afflicted by diabetes, a biosensor tuned to physiological concentrations of glucose in the millimolar range is a clear advantage, which is taught at page 53, lines 11-20, of the specification. As shown in Table 5 of the present specification, decreased binding affinity is achieved by attaching a reporter group at position 183 of glucose binding protein. See page 35 of the specification. In Table 5, it can also be seen that the fluorescence characteristics ΔI_{std} and ΔR_{max} are desirable.

Fig. 5A shows that fluorescence response to log concentrations of glucose is linear. By ratiometry, clinically relevant ranges of glucose may be measured and different clinical states easily distinguished as shown in Fig. 8A. These unexpected results are not taught or rendered obvious by the prior art of record. Further, there is no reasonable expectation of success found in the cited documents to attach a reporter group at position 10, 93 or 183 of GBP such that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as recited in the present claims.

The Examiner alleged that the ΔI_{std} and ΔR_{max} properties of Hellinga's and Amiss' biosensors would necessarily be the same because "the mere recognition of inherent properties in the prior art does not render nonobvious an otherwise known invention." This allegation is incorrect in the context of Applicants' claimed invention. These are not Section 102 rejections. Thus, the biosensors of the cited documents are clearly not the same as the presently claimed biosensors. There is no other basis in the Office Action for assuming the ΔI_{std} and ΔR_{max} properties required by claims 11-14 are inherent in the biosensors disclosed in Hellinga and Amiss because they are necessarily different as compared to the presently claimed biosensors. Moreover, no evidence or reasoning was presented in the Office Action that these properties were known or predictable at the time Applicants' invention was made.

The Examiner also provided no evidence that there was a reasonable expectation of success to attach a reporter group at any position within GBP such that "binding of glucose in a glucose-binding pocket of said biosensor causes a change in signaling by said reporter group" as required by the present claims.

Therefore, lacking both an acceptable reason for attaching a reporter group at specific positions within GBP and a reasonable expectation of success that they would be suitable as biosensors, a prima facie case of obviousness was not established.

For the above reasons, withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinary skill in the art when this invention was made.

35 U.S.C. 112 – Definiteness

Claims 1-2, 7-15 and 31-32 were rejected under Section 112, second paragraph, as allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The term "position" refers to the amino acid sequence of the bPBP. The '627 patent is cited for describing *E. coli* periplasmic binding proteins, including the amino acid sequence of glucose binding protein (GBP), on page 2, lines 3-6, of the present specification. Its contents are incorporated by reference on page 57, lines 11-14, of the present specification. A specification need not teach, and preferably omits, what is well known in the art. See *Hybritech v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

No specific reference to a sequence identifier is required because the GBP's are known in the art. The recitation of GBP's amino acid sequence is also not necessary because numbering of their positions is well known in the art and would be understood by the skilled artisan. For example, recitation of GBP's amino acid sequence was not required for the Examiner to thoroughly search the subject matter of the claims.

Therefore, withdrawal of the indefiniteness rejection is requested.

35 U.S.C. 112 – Written Description

The specification must convey with reasonable clarity to persons skilled in the art that applicant was in possession of the claimed invention as of the filing date sought. See *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). But the Patent Office has the initial burden of presenting evidence or a reason why persons of ordinary skill in the art would not have recognized such a description of the claimed invention in the original disclosure. See *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989).

Claims 1-2, 7-14 and 31-32 were rejected under Section 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants traverse because the specification teaches a representative number of species (i.e., specific biosensors) within the claimed genus. The guidance that the Examiner alleges would be required but is absent from this specification would have been known to a person skilled in the art at the time this application was filed.

As discussed above with respect to the indefiniteness rejection, the requirements of Section 112 are satisfied by the present specification and claims without providing a "baseline sequence" for GBP as alleged on page 21 of the Office Action. US 6,277,627 is cited for describing *E. coli* periplasmic binding proteins, including the amino acid sequence of glucose binding protein (GBP), on page 2, lines 3-6, of the present specification. Its contents are also incorporated by reference on page 57, lines 11-14, of the present specification. A specification need not teach, and preferably omits, what is well known in the art. See *Hybritech* at 94.

No specific reference to a sequence identifier is required because the GBP's are known in the art. The recitation of GBP's amino acid sequence is also not necessary because numbering of their positions is well known in the art and would be understood by the skilled artisan. For example, recitation of GBP's amino acid sequence was not required for the Examiner to thoroughly search the subject matter of the claims.
The amino acid sequence of glucose binding protein (GBP) is not required to be recited

Therefore, withdrawal of the written description rejection is requested.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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